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Seroepidemiological Reconstruction of Long-term Chikungunya Virus Circulation in Burkina Faso and Gabon

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Chikungunya virus (CHIKV) is a major public health concern worldwide. However, infection levels are rarely known, especially in Africa. We recruited individuals from Ouagadougou, Burkina Faso and Lambaréné, Gabon (age range, 1–55 years), tested their blood for CHIKV antibodies, and used serocatalytic models to reconstruct epidemiological histories. In Ouagadougou, 291 of 999 (29.1%) individuals were seropositive, ranging from 2% among those aged <10 years to 66% in those aged 40–55 years. We estimated there were 7 outbreaks since the 1970s but none since 2001, resulting in 600 000 infections in the city, none of which were reported. However, we could not definitively conclude whether infections were due to CHIKV or o'nyong-nyong, another alphavirus. In Lambaréné, 117 of 427 (27%) participants were seropositive. Our model identified a single outbreak sometime since 2007, consistent with the only reported CHIKV outbreak in the country. These findings suggest sporadic outbreaks in these settings and that the burden remains undetected or incorrectly attributed.

Keywords. chikungunya; Africa; Burkina Faso; Gabon; seroepidemiology.

Chikungunya virus (CHIKV) is an alphavirus in the family *Togaviridae*, transmitted by *Aedes* mosquitoes. Infection by CHIKV is associated with acute onset of fever, joint pain, headache, muscle pain, and rash [1–4]. It can also result in severe chronic arthralgia that can last for months or even years [5, 6]. Initially identified in Tanzania in 1952, autochthonous transmission of CHIKV has now been recorded in 6 continents with recent large-scale epidemics in Asia and the Americas [7, 8].

The timing and location of CHIKV outbreaks appear to be unpredictable [9]. Furthermore, in global tropical and subtropical countries, there are other common causes of acute febrile illness with similar clinical presentations, such as dengue virus

(DENV) and Zika virus (ZIKV) [10, 11]. Without adequate diagnostic assays, differential diagnosis of acute febrile illness is challenging and misdiagnosis of chikungunya as dengue or other viral infections is common [11, 12]. Collectively, these factors mean that entire CHIKV outbreaks may be missed, leading to the underestimation of the global burden from chikungunya. For example, a recent seroepidemiological study in the Philippines estimated that, over a 60-year period, 350 000 CHIKV infections had occurred in 4 separate short-lived outbreaks but only a single case had ever been recorded [9].

In Africa, the continent where CHIKV was first identified and apparently evolved, the accurate assessment of chikungunya burden is particularly challenging. Most African countries lack an established disease surveillance reporting system for chikungunya, and diagnostic assays for CHIKV are not widely available. Since the first report of CHIKV in Tanzania, there have been reports of periodic outbreaks in multiple locations in Africa [13]. However, without systematic surveillance systems that can reliably and consistently capture outbreaks, the long-term epidemiology of CHIKV in the continent remains poorly understood. In addition, distinguishing antibodies resulting from CHIKV infection, as opposed to the close African alphavirus relative o'nyong-nyong virus (ONNV), is technically challenging [14]. The introduction of CHIKV into the Americas was followed by rapid dispersal throughout the

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continent, with virtually all countries affected—it remains unknown if such near synchrony in CHIKV epidemiology is present in Africa. Burkina Faso, a country in West Africa, has never reported cases of chikungunya. However, the presence of *Aedes* mosquitoes has been documented in the region alongside reports of cases of other *Aedes*-transmitted viruses, suggesting that environmental conditions are supportive for CHIKV transmission [15]. Farther south, in Gabon, an outbreak of chikungunya was reported in 2007; however, it is unknown whether the virus circulated prior to this date.

In this context, mathematical models applied to cross-sectional seroprevalence surveys can help understand the historic circulation of CHIKV transmission [9]. Individuals exposed to CHIKV develop long-lived antibodies specific to the virus that can subsequently be detected using serological assays. Here, we reconstruct the historical circulation of CHIKV over a 50-year period using serological surveys from 2 locations in Africa, Burkina Faso and Gabon.

METHODS

Study Areas and Populations

We conducted population-based serological surveys using baseline blood samples from cohorts in Ouagadougou, Burkina Faso, and Lambaréné, Gabon (Figure 1).

Ouagadougou is Burkina Faso's largest city, with a population of 2 741 128, and 45% of the population is <15 years of age. In 2015, we established a cohort of 3026 individuals. We randomly selected household points using information from the

geographic information system database of houses in the study area. Study teams then visited the preselected households and recruited individuals between 1 and 55 years of age. Participants underwent phlebotomy (5 mL for children and 7 mL for adults) by trained field team staff and completed a questionnaire that asked information on age and basic demographic information. The enrollment bleed took place in May–June 2015.

In Gabon, our catchment area population was the 70 000 residents of Lambaréné and its surroundings in Moyen-Ogooué province. The majority of Lambaréné residents live in semirural areas. The population in Lambaréné is relatively young with about 50% <20 years of age. In 2015, we established a cohort of 3022 individuals in Lambaréné. Study teams made home visits, accompanied by community/village health workers who are familiar with the villages and their residents. The field team screened houses in the selected villages by knocking on doors of every 5–7 houses, depending on the household density per neighborhood. In the selected households, we invited individuals aged 1–55 years to participate in the study. Participants in the study underwent phlebotomy (5 mL for children and 7 mL for adults). Serosurvey questionnaires were administered at the household by trained field team staff. The enrollment bleed took place in November–December 2015.

Serological Testing

We used an in-house Luminex-based multiplex immunoassay (arbo-MIA) developed by the Institut Pasteur to detect immunoglobulin G antibodies to the E1 CHIKV protein. This multiplex assay has previously been used for the detection of historic Zika virus infection, as well as other flaviviruses, including West Nile virus, Japanese encephalitis virus, and tick-borne encephalitis virus in horses [16–18]. As we did not have the budget or capacity to test all samples, we selected a random subset from each location for the serological testing. In Ouagadougou, we randomly selected 1000 samples from the 3026 enrollment blood draws to undergo Luminex-based multiplex immunoassay testing. The test from one individual failed. We therefore include the results from 999 individuals in the analysis. In Lambaréné, we randomly selected 427 samples from the 3022 enrollment blood samples for testing by the same Luminex assay. All testing was performed at the International Vaccine Institute, Seoul, Korea. We also tested a random subset of 55 samples from Burkina Faso (44 detected as being seropositive to CHIKV and 11 detected as being seronegative using arbo-MIA) using a plaque reduction neutralization test (PRNT) conducted at the University of Texas Medical Branch facilities. We were not able to test all samples using the PRNT due to budget constraints. We tested neutralization capacity to both ONNV and CHIKV and identified the 80% reduction (PRNT₈₀) titer for each serum. We considered a PRNT₈₀ value >10 to be positive.

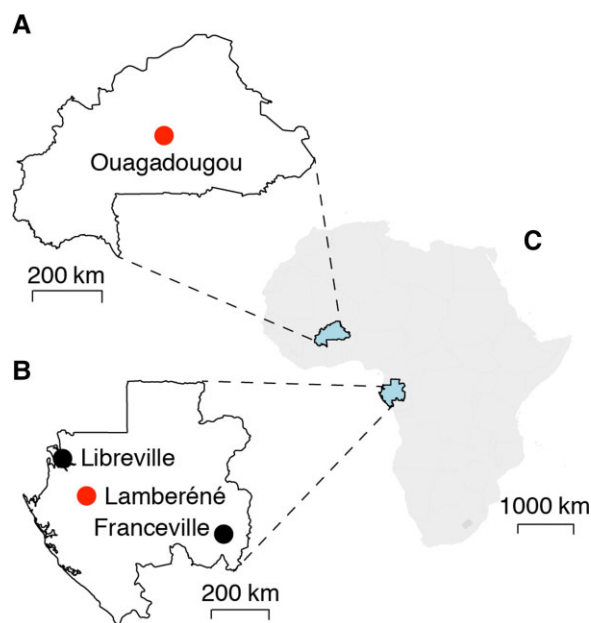


Figure 1. Map of study locations. A, Ouagadougou, Burkina Faso. B, Lambaréné, Gabon. C, Locator map of Africa.

Passive Surveillance

In addition to the cohort participants, we conducted passive facility-based fever surveillance studies in the same catchment area in both locations. In Burkina Faso, the surveillance study was initiated in December 2014 in 5 selected primary health-care centers in the municipality of Ouagadougou [19]. In Gabon, the surveillance study was initiated in May 2015 at the Albert Schweitzer Hospital in Lambaréné. Residents, aged between 1 and 55 years, presenting at both outpatients and inpatient departments with current fever (axillary temperature $\geq 37.5^{\circ}\text{C}$) or history of fever for ≤ 7 days duration without localizing signs (fever caused by a localized infection as well as fever with a known and confirmed etiology, such as malaria confirmed by malaria rapid diagnostic test) were enrolled.

From this passive surveillance system, to identify the etiology of the illnesses, we tested 157 acute samples collected from febrile patients in Ouagadougou, and 64 acute samples collected from febrile patients in Lambaréné, using Bioneer AccuPower ZIKV/DENV/CHIKV multiplex real-time reverse-transcription polymerase chain reaction (RT-PCR) commercial kit.

Statistical Analysis

For pathogens such as CHIKV that induce long-lived immunity, the proportion of individuals who are seropositive as a function of age can be used to reconstruct the historical patterns of infection within a community [9, 20, 21]. We reconstructed the historic force of infection (the annual probability of infection) for each year between 1960 and 2015 using a Markov chain Monte Carlo (MCMC) framework as previously described [9]. In brief, age can be used as a marker of the total time of infection risk. By assuming that infection risk is independent of age, we can calculate the likelihood of the annual probability of infection in susceptible individuals who were alive over the period of interest (here between 1970 and 2015). Prior to 1970, there were too few individuals who were alive in our dataset at the time. We assumed a constant probability of infection prior to 1970. We used a Bayesian MCMC framework using RStan to estimate the annual force of infection in each location [22]. We ran 4 chains of 3000 iterations for each of the 2 sites, removing 33% of iterations for burnin. This approach assumes that antibody titers remain detectable many years after infection. This is consistent with what has been observed in the Philippines, where CHIKV titers appeared to remain high decades after infection [9, 23]. This approach also assumes lifelong immunity following infection. In the event that 1 or more of the outbreaks were caused by a related cross-reactive alphavirus such as ONNV, this approach would assume that there was cross-immunity between the viruses.

We used a bimodal prior for the annual force of infections using a mixture of normal distributions, 1 centered at 0 with a standard deviation (SD) of 0.001 and 1 centered at 0.5 with an SD of 0.1. This approach allowed the model to efficiently

have either no outbreak in a year or to have an outbreak with a nonnegligible proportion of the population infected. In post hoc analyses, we defined outbreaks as having at least 5% of the population infected. This allowed us to estimate the number of outbreak years per model iteration and the probability of having an outbreak per year. We separately fit models in each location where we assumed a constant annual force of infection.

Reconstruction Proportion Infected by Year

We used the age-specific distribution of the population over time in both countries to estimate the proportion of the population susceptible to CHIKV in any year (age pyramids for each country are available from the US State Department). We assume that all individuals were susceptible in 1960. We then use the estimated force of infection by year to calculate the proportion of the population that become infected and therefore subsequently immune each year.

Ethical Considerations

Written informed consent, and assent for participants 7–17 years of age, was obtained from patients by study staff. The protocol for each study obtained ethical approvals from the institutional review boards (IRBs) of the International Vaccine Institute, the London School of Hygiene and Tropical Medicine, and the ethics committee of host country institutions, including the IRB of Centre Hospitalier de l'Université de Montréal at the University of Montreal, and the National Health Ethical Committee of Burkina Faso, Gabon National Ethics Committee and Institutional Ethics Committee, and Scientific Review Board of Centre de Recherches Médicales de Lambaréné in Gabon.

RESULTS

Of the 999 individuals included in the sample set from Burkina Faso, the mean age was 22.8 and 620 (62%) were female (Table 1). We found that 291 had evidence of historic infection (29%). The probability of being seropositive differed by sex, with 33% of female participants being seropositive compared to 23% of males, giving a relative risk of being seropositive if female of 1.39 compared to males (95% confidence interval [CI], 1.12–1.72); ($P = .002$ for difference). We observed significant heterogeneity in seropositivity by age with 5 seropositive individuals <10 years of age (2%) compared to 66% seropositive in those 40–55 years old. Our models that reconstructed the past circulation estimated a median of 7 outbreaks since 1970, with an average of 23% of the population infected per outbreak (range, 0.10–0.43) and a mean gap of 7.8 years between outbreaks. Outbreaks appeared concentrated in the early 1970s, early 1980s, early 1990s, and early 2000s (Figure 2A). There was no evidence of any transmission since 2001. Using

Table 1. Age, Sex, and Serostatus of Participants

Characteristic	Burkina Faso			Gabon		
	Seropositive	Seronegative	Total	Seropositive	Seronegative	Total
Age group, y						
1–4	1	60	61	4	44	48
5–9	4	139	143	27	54	81
10–14	7	137	144	26	53	79
15–19	16	108	124	11	35	46
20–24	36	78	114	5	36	41
25–29	49	67	116	14	22	36
30–34	34	39	73	8	12	20
35–39	38	26	64	8	16	24
40–44	33	20	53	5	16	21
45–49	30	18	48	6	10	16
50–55	43	16	59	3	12	15
Total	291	708	999	117	310	427
Sex						
Male	202	418	620	72	203	275
Female	89	290	379	45	107	152
Total	291	708	999	117	310	427

the historical age structure of the population, we were able to estimate the proportion of the population that was susceptible through time (Figure 2C). We found that around half of the population has remained susceptible since the 1970s, rising to 71% (95% CI, 70%–73%) by 2014.

In Gabon, the mean age of individuals in the sample set was 19.2 and 275 of 427 (64%) were female (Table 1). We found that 117 of 427 (27%) of the study population had been infected, with little difference by age group. In female participants, the probability of being seropositive was 26% compared to 30% in males, giving a relative risk of being seropositive if female of 0.88 (95% CI, .65–1.21) ($P = .50$ for difference). Using models fit to the seropositivity by age, we found that there had been no circulation prior to 2007, with an estimated single outbreak sometime between 2007 and 2014, where 29% of the population was infected (95% CI, 25%–34%) (Figure 2B). We found no evidence of introductions prior to this time. We estimate that in 2015, 70% of the population was susceptible to CHIKV (Figure 2D). In both locations, our models were able to reconstruct the observed seropositivity by age (Figure 2E and 2F). Models that assumed a constant force of infection resulted in a worse fit (Supplementary Figure 1).

We found that the PRNT₈₀ titers to CHIKV correlated well to the arbo-MIA titers (Pearson correlation coefficient [ρ] = 0.78) (Figure 3). However, consistent with previous findings [24], we found that samples that were seropositive to CHIKV also had high titers to ONNV, with a high correlation between CHIKV arbo-MIA titers and ONNV PRNTs ($\rho = 0.80$) as well as between CHIKV and ONNV PRNT titers ($\rho = 0.88$). Among the 44 individuals that had detectable CHIKV titers as per the arbo-MIA assay, 42 (95%) had detectable PRNT titers to both CHIKV and ONNV, 1 (2%) had detectable titers to only

ONNV and none had only detectable titers to CHIKV. None of the samples that were considered seronegative by arbo-MIA had detectable PRNT titers to either ONNV or CHIKV. Among individuals with any detectable PRNT titers, PRNT titers were higher to ONNV (mean, 549) than CHIKV (mean, 294).

We also used the results of the PRNT testing to assess the performance of the arbo-MIA assay. If we consider detectable CHIKV PRNT titers as the gold standard, we find that using our cutoff of 4 to define seropositivity resulted in a sensitivity of 1.0 and a specificity of 0.79 for the arbo-MIA assay and an area under the curve of 0.94 (Supplementary Figures 2 and 3).

Alongside the cohort samples, we tested 157 acute samples collected from febrile patients in health facilities in Ouagadougou, and 64 acute samples collected from febrile patients in health facilities in Lambaréné using a ZIKV/DENV/CHIKV multiplex real-time RT-PCR. We found that none of these acute samples was positive for CHIKV, consistent with no transmission of CHIKV in 2015 in either location.

DISCUSSION

We have used the results of seroprevalence studies conducted in 2 African countries to reconstruct the long-term historical circulation of CHIKV. Despite similar levels of overall seropositivity, we identified 2 completely different patterns of past circulation in the 2 countries. We found evidence of several introductions into Burkina Faso since the 1970s but no circulation since 2003. Lambaréné in Gabon, by contrast, had no evidence of circulation prior to 2007.

There are other alphaviruses in Africa. In particular, ONNV has been identified in a number of countries, although not in

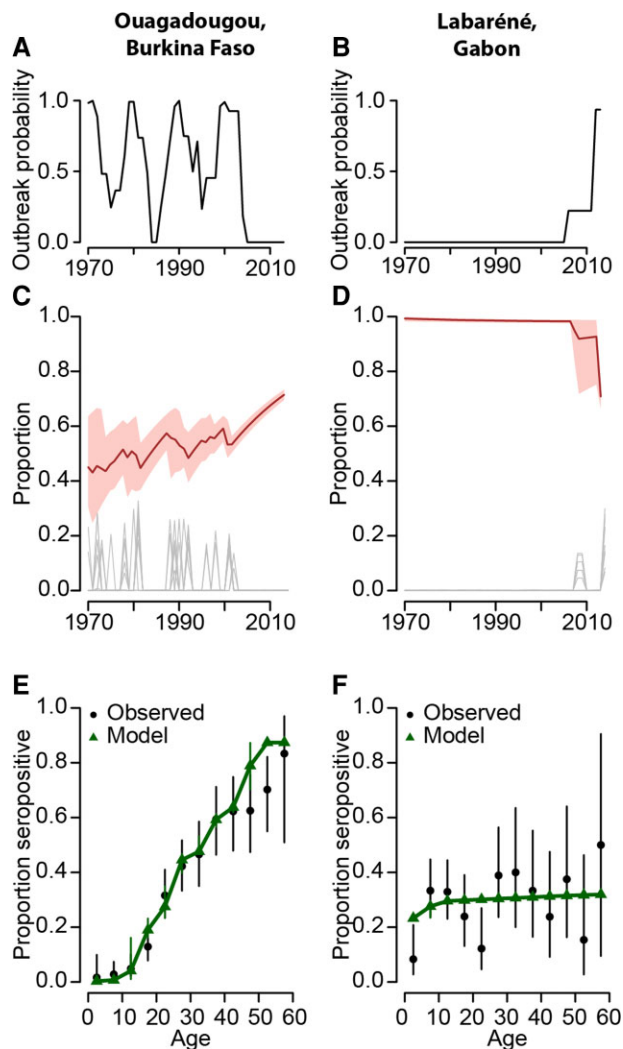


Figure 2. Serocatalytic model results. *A* and *B*, Estimated probability of an outbreak over rolling 5-year windows for Ouagadougou, Burkina Faso and Labaréné, Gabon. Outbreak probabilities are calculated as the proportion of model iterations that have an annual force of infection of at least 0.05 in any year over each 5-year window between 1970 and 2015. *C* and *D*, Estimated proportion of population susceptible by year (red) with 95% confidence intervals (shaded region). The gray lines represent 10 randomly selected reconstructions of the probability of infection by year. *E* and *F*, The observed (black dots and 95% confidence intervals) and fitted (green line) for the proportion seropositive by 5-year age groups for the 2 locations.

Burkina Faso or Gabon [14, 25]. Most of our CHIKV-seropositive samples from Burkina Faso were also seropositive to ONNV. It was not surprising to find that these sera were strongly neutralized by both viruses because these viruses are close relatives with known cross-neutralization [24]. While the higher PRNT titers for ONNV compared to CHIKV seen for many samples suggest that ONNV may have infected at least some of these persons, cross-neutralization titers for these viruses can sometimes be higher than for homologous neutralization [26], possibly reflecting original antigenic sin. Furthermore, previous modeling exercises have suggested

that CHIKV infection induces an ONNV neutralization response in 80% of instances whereas an ONNV infection leads to a cross-reactive CHIKV response in only 22% of cases [14]. Overall, firm conclusions are difficult to reach without information on which of the viruses circulate in a given region. Our inability to firmly conclude the pathogen responsible for the outbreaks in Burkina Faso highlights the need to obtain more specific serological assays that can discriminate between closely related viruses. Despite this uncertainty, the timing and the size of the outbreaks we identified would still be informative for other arboviruses. The timing of the inferred single outbreak in Gabon is consistent with reports of a large CHIKV outbreak in the country, suggesting that the seropositive samples from Gabon were due to CHIKV [4].

In Burkina Faso, we observed a significant difference in the probability of being seropositive by sex, with females around 1.4 times more likely to have been infected than males. This finding is consistent with previous work in Bangladesh that found that females were 1.5 times more likely to be infected, with the difference in risk attributed to females spending more time in and around the home, where *Aedes aegypti* mosquitoes, the main peridomestic or urban vectors, tend to be found [27]. Increased risk of CHIKV infection among females has also been observed in Mali [14]. Unlike CHIKV, ONNV is spread by anopheline mosquitoes, which primarily feed at night, when there are unlikely to be major differences in the risk of exposure by sex [28]. This suggests that at least some of the outbreaks in Burkina Faso were due to urban CHIKV. We did not find a difference in risk of infection by sex in Gabon. An increased understanding of behavioral differences by sex, and exposure patterns to different mosquito species in these settings, may help explain these heterogeneities in infection risk.

The distribution of both enzootic (sylvatic) and urban CHIKV remains poorly delineated in Africa, with the exception of Senegal where both cycles have been documented [29]. There have been no historical reports of CHIKV or ONNV in Burkina Faso. Our findings therefore suggest several unreported epidemics sweeping through the country over a 40-year period. Using the size of the Ouagadougou population over time and the estimated susceptible population in each year (which has increased from 60 000 in 1960 to >2 million today), we can estimate that these unreported epidemics infected 600 000 individuals over the 40-year period. Chikungunya was first reported in Gabon in 2007. Further outbreaks were subsequently detected in 2010. While we cannot precisely identify when CHIKV first arrived in Lambaréné, we provide strong evidence that there was no circulation prior to 2007. Our study suggests that around 30% of the 70 000 residents in Lambaréné and its surroundings were infected during this outbreak.

The lack of historic synchrony in epidemic timings across our 2 locations suggests that historically at least, localized risk

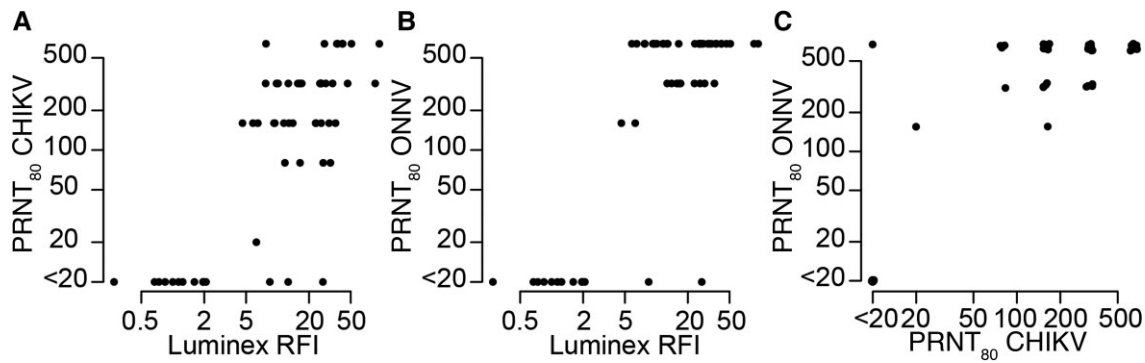


Figure 3. Comparison of chikungunya virus (CHIKV) multiplex immunoassay (arbo-MIA) with CHIKV and o'nyong-nyong virus (ONNV) plaque reduction neutralization test (PRNT) titers (N = 55). *A*, Comparison of Luminex (arbo-MIA) CHIKV relative fluorescence intensity (RFI) with 80% reduction (PRNT₈₀) CHIKV neutralization titers among 55 individuals where both assays were conducted. *B*, Comparison between CHIKV RFI with PRNT₈₀ ONNV neutralization titers. *C*, Comparison between CHIKV and ONNV neutralization titers.

factors rather than pan-continental disease drivers determined CHIKV epidemiology. Human mobility appears key to CHIKV spread [27, 30]. As the flow of populations across borders increases in Africa, this may lead to greater interdependence between locations, such as was observed in the CHIKV and ZIKV epidemics in South America [31].

Our study highlights the ability of alphaviruses to infect a substantial proportion of the population during epidemics without being detected. From a clinical perspective, chikungunya can appear very similar to other diseases, including dengue, influenza, and malaria. Without the widespread access to testing, it seems unlikely that this trend will change. However, by integrating basic mathematical models into cross-sectional seroprevalence studies, we can understand historical circulation patterns and estimate the size of the population that remains susceptible. It is notable that crude levels of seropositivity were very similar in the 2 countries. It was only by exploring patterns of seropositivity by age that we could identify the different experiences in the 2 settings.

The study has some limitations. We recruited more female participants than males in both locations. This difference is likely due to women being more likely to be at home during the day, when study teams visited homes. Working males may have underlying different exposure profiles that could alter their risk of infection. In addition, the study design meant we did not recruit older individuals, so we could not identify outbreaks going further back than the 1970s. Finally, we did not have the capacity to test all samples by neutralization assay. Increased testing may allow more fine-scale understanding of the risk of infection by different alphaviruses, as has previously been conducted elsewhere [14].

This study highlights the potential of cross-sectional serostudies to complement case-based surveillance studies. They allow us to characterize the underlying, often hidden, burden of infection in communities as well as understand the patterns of

emergence and spread. In these settings, CHIKV epidemiology appears to be characterized by short-lived outbreaks with long interepidemic periods.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. H. S. reports being a paid consultant to Gavi, the Vaccine Alliance, for work understanding the potential of chikungunya vaccines. All other authors report no potential conflicts. Funding to pay the Open Access publication charges for this article was provided by the University of Cambridge.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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